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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,999	06/08/2001	Maxime Ranger	2267.001	1762

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MCHALE & SLAVIN, P.A.
2855 PGA BLVD
PALM BEACH GARDENS, FL 33410

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,999	RANGER ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9 and 11-18* is/are pending in the application.

4a) Of the above claim(s) *15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-4,6-9 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/20/04 has been entered.

Claim 19 was canceled as requested.

Claims 1-4, 6-9, and 11-18 are pending. Claims 15-18 were withdrawn from consideration in Paper No. 10 as being drawn to a non-elected invention. Applicant timely traversed the restriction requirement in Paper No. 8.

Claims 1-4, 6-9, and 11-14 are under consideration in this Office Action.

Rejections and Objections Overcome

Applicants amendments were sufficient to overcome the rejections under 35 USC 112, second paragraph and 35 USC 102, set forth in the previous Office Action.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6-9 and 11-14 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 09/878,115. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claims 1-14 of the '115 application are drawn to unimolecular polymeric micelles comprising an ionizable inner core and a hydrophilic outer shell wherein said ionizable inner core includes ionizable repeating units in combination with non-ionic hydrophobic repeating units and wherein said ionizable repeating units include at least one compound selected from the group consisting of alkylacrylic acid derivatives, acrylic acid derivatives, aminoalkylacrylate derivatives, and (aminoalkyl) alkylacrylate derivatives, wherein said hydrophobic repeating units include at least one compound selected from the group consisting of acrylate derivatives, acrylamide derivatives, alkylacrylate derivatives, alkylacrylamide derivatives, arylacrylate derivatives and arylacrylamide derivatives; and wherein said hydrophilic outer shell is not cross-linked and originates from functionalized and hydrophilic polymers and includes at least one hydrophilic compound selected from the group consisting of vinyl monomers, vinyl

oligomers and vinyl polymers. As such, the claims of '115 are drawn to species of the instantly claimed genus, and the instant claims are obvious in view of them.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6-9, and 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 6-9, and 11-14 are indefinite in their recitation of "water soluble supramolecular self assemblies". As a term of art, "supramolecular self assemblies" would clearly be understood to comprise any complex of two or more molecules, such that the instant claims would embrace any water soluble complex consisting essentially of at least two of the recited copolymers. However, Applicant is entitled to be his own lexicographer, and at paragraph [0036] the specification states that "[i]n the present invention, the terms "water-soluble self-assemblies" and "micelles" are equally employed although the proposed structures may not necessarily correspond to the true definition of micelles." As a result it is unclear which structures are within the metes and bounds of the claims and which are not. To the extent that it is unclear what is the

structure of a "water soluble supramolecular self assembly" it is also unclear what is a "core" of such an assembly, as recited in the final clause of the claim

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1-4, 6-9, and 11-14, readable on a genus of water soluble supramolecular self-assemblies of a polyelectrolyte comprising a generic hydrophilic outer shell, and a generic polyelectrolyte core comprising both ionizable and hydrophobic residues, which not only must exhibit the ability to formulate a water soluble supramolecular self-assembly, but also to able to trigger a release of a pharmaceutical agent by altering the ionization state of the assembly core, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors), at the time the application was filed, had possession of the claimed invention.

The claimed invention relates to polymeric water soluble supramolecular self-assemblies of a polyelectrolyte consisting essentially of diblock, multiblock or random block copolymers comprising a hydrophobic block containing ionizable or charged units, in combination with non-ionic hydrophobic units, wherein a polyelectrolyte segment comprising non-ionic hydrophobic units forms a core of the assembly. As discussed above, the breadth of the genus of embraced assemblies is unclear because the metes

and bounds of "water soluble supramolecular self assemblies" are unclear. In one embodiment, the polyelectrolyte core elements can be rendered hydrophobic by counter ion-mediated charge neutralization, thereby allowing micelle formation. The specification teaches that micelles comprising the copolymers may be destabilized by inducing ionization of the hydrophobic polyelectrolyte core, thereby allowing delivery of drugs sequestered therein. The essence of the invention is the stabilization of the supramolecular self-assemblies by inclusion of hydrophobic, non-ionizable monomers within the polyelectrolyte portion of the copolymer.

With respect to the issue of a generic water soluble self assembly consisting essentially of a polyelectrolyte, the specification teaches the formation of micelles comprising the recited polyelectrolytes. However, the genus of water soluble self assemblies comprises a vast breadth of structures that includes liposomes, hexagonal arrays, and any soluble structure containing two or more of the recited polyelectrolytes. However, the specification discloses only the formation of micelles, and lacks any disclosure of any other defined supramolecular self assembly.

With respect to the issue of a generic polyelectrolyte core comprising both ionizable and hydrophobic residues as claimed, it is acknowledged that the as-filed specification discloses sufficiently an ionizable core composed of ionizable repeating monomers in combination non-ionic hydrophobic repeating monomers, wherein the ionizable repeating monomers include at least one compound selected from the group consisting of alkylacrylic acids and derivatives, aminoalkylacrylates and derivatives, and (aminoalkyl) alkylacrylates and derivatives, and wherein the non-ionic hydrophobic

repeating monomers include a hydrophobic vinyl compound. With respect to the issue of a generic hydrophilic outer shell, the as-filed specification discloses sufficiently a hydrophilic shell composed of functionalized and hydrophilic block-copolymers comprising repeating vinyl monomers. However, the as-filed specification does not provide sufficient written description of any other representative number of species other than the limited species as indicate above.

Present claims relate to an extremely large number of possible water soluble supramolecular self-assemblies that must exhibit the biological properties as contemplated by the as-filed specification. The as-filed description coupled with the state of the prior art only provide sufficient description of micelle based block-copolymer comprising repeating vinyl monomers on the hydrophilic shell and an ionizable core composed of ionizable repeating monomers alone or in combination with non-ionic hydrophobic repeating monomers, wherein the ionizable repeating monomers include at least one compound selected from the group consisting of alkylacrylic acid derivatives, acrylic acid derivatives, aminoalkylacrylate derivatives, and (aminoalkyl) alkylacrylate derivatives, and wherein the non-ionic hydrophobic repeating monomers include a hydrophobic vinyl compound. Thus, it is apparent that on the basis of Applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays and/or any other unspecified structure containing unspecified compounds that are yet to be discovered but embraced the claimed invention, wherein the detailed and a substantially and specifically common structure of

the genera of the claimed compounds were not described; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structure(s) of component(s) that are linked structurally to the extent that the described structures with essential elements must be able to reflect any of the disclosed biological functions as contemplated by the as-filed specification. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming unspecified molecular structures of materials) or claiming compounds without an adequate written description of essential elements of the compounds in order to exhibit applicant's intended claimed property, e.g. trigger a release of a pharmaceutical agent by altering the ionization state of the micelle core contained within a hydrophilic shell, without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See Fiers v. Revel, 25 USPQ2d 1601 (CA FC 1993) and Regents of the Univ. Calif. v. Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art could recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics. Inc., 48 USPQ2d 1641, 1646 (1998). Thus, in view of the reasons set forth above, one skilled in the art at the time the

invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Enablement

Claims 1-4, 6-9, and 11-14 are rejected under 35 U.S.C. 1 12, first paragraph, because the specification is enabling only for claims limited to: micelles consisting essentially of a polyelectrolyte block copolymer comprising at least one ionizable but hydrophobic block composed of ionizable repeating monomers in combination with non-ionic hydrophobic repeating monomers, and at least one hydrophilic block, wherein said hydrophilic block comprises a functionalized and hydrophilic polymer comprising repeating vinyl monomers, wherein the ionizable repeating monomers include at least one compound selected from the group consisting of alkylacrylic acid derivatives, acrylic acid derivatives, aminoalkylacrylate derivatives, and (amino alkyl) alkylacrylate derivatives, and wherein the non-ionic hydrophobic repeating monomers include a hydrophobic vinyl compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior

art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description for possessing of the genus of water soluble supramolecular self-assemblies of a polyelectrolyte, particularly in view of the reasons set forth above, one skilled in the art would not known how to use and make the claimed invention so that it would operate as intended within the context of applicant's claimed invention.

Furthermore, the state of the prior art exemplified by Benahmed (Pharmaceutical Research, Vol. 18, No. 3, 2001, pp. 323-328) states that polymeric micelles are generally prepared from amphiphilic diblock or multiblock copolymers, that most studies dealt with the preparation or the use of PEG or PVP for the making of a hydrophilic shell, and that hydrophobic vinyl compounds are employed to make a hydrophobic core (page 323, column 1-2). In addition, Jones et al. (European J. of Pharm. Biopharm. 48, 101-11 1, 1999) further states that polymeric micelles are characterized by a core-shell structure, and that pharmaceutical research on polymeric micelles has been mainly focused on copolymers having an A-B diblock structure with A, the hydrophilic shell) and B, the hydrophobic polymers (core, respectively). The presently pending claims embrace an enormous number of supramolecular self-assemblies, which are not limited to those stated in the prior art and exemplified in the as-filed specification. Given the state of the prior art, the breadth of the claims, the nature of the invention, the lack of working examples and/or guidance for the making of unimolecular micelles other than

those deemed to be enabling, it is not apparent how a skilled partisan, without any undue experimentation, practices the full scope of the claimed invention as pending.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Heller et al (J. Pharm. Sci. 88(1): 58-64, 1999) as evidenced by Stryer (In *Biochemistry*, Fourth edition, W.H. Freeman and Co., New York), GenBank Accession No. AAA21101, published 8/6/1994) and GenBank Accession No. CAA23748, published 4/24/1993).

Heller teaches polyethylene glycol (PEG) modified hemoglobin.

Stryer teaches that human hemoglobin is a four subunit protein composed of 2 alpha globin and 2 beta globin subunits. See pages 154 and 155.

GenBank Accession No. AAA21101 shows that human beta globin comprises both hydrophobic and ionizable monomers, e.g. the first 10 amino acids include four hydrophobic residues (M, V, L, and P), and 4 ionizable residues (H, E, E, and K).

GenBank Accession No. CAA23748 shows that human alpha globin comprises both hydrophobic and ionizable monomers, e.g. the first 10 amino acids include four hydrophobic residues (M, V, L, and P), and 2 ionizable residues (D and K).

As such, Heller teaches a water soluble supramolecular assembly of a polyelectrolyte. The composition can be considered to be a random copolymer with grafted hydrophilic, nonionic PEG groups. The composition can be considered to comprise a pharmaceutical constituent, which is a drug, i.e. the iron atoms in the heme porphyrins.

Thus Heller anticipates the claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.

Richard Schnizer, Ph.D.